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RESISTANT PLASMODIUM FALCIPARUM INFECTION FROM SAMARINDA, KALIMANTAN

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Rumah Sakit Caltex di Rumbai, Pekanbaru pernah melaporkan adanya P. falciparum yang resistent terhadap chloroquine. Setelah dilakukan follow up ternyata kasus ini masih sangat sensitive terhadap group 4 aminoquinoline.

Pada tahun 1973, seorang dokter yang bekerja untuk suatu pabrik obat menyebar luaskan desas-desus adanya P. vivax yang resistent terhadap chloroquine.

Pembuktian penyelidikan oleh team Indonesia dan U.S.A. Naval Medical Research Unit -2 Jakarta, pada bulan Oktober 1973, ternyata P. vivax ditempat yang sama masih sensitive terhadap chloroquine.

Kasus pertama P. falciparum yang resistent terhadap 4 aminoquinoline ditemukan pada infeksi yang terjadi didekat Samarinda, Kalimantan Timur.

Berdasar WHO – Sensitivity test, ternyata bahwa pada kasus tersebut terdapat adanya asexual parasite resistent tingkat resistent I terhadap standard dosis dari 1.500 mg amodiaquine base dan standard dosis dari 1.500 mg chloroquine base.

Resistance of *Plasmodium falciparum* to chloroquine in Indonesia was mentioned by Peters[3], "In the region of Pekanbaru in the island of Sumatra at least one RI response appears certain, but other patients with acute falciparum malaria have responded normally to chloroquine therapy". This information originated from the Caltex hospital in Rumbai, Pekanbaru. In fact, follow-up of *P.falciparum* infections treated in this hospital shows that all were fully sensitive to 4-aminoquinolines ang that the above statement, based on a misunderstanding, should be disregarded.

More recently (1973) rumors of *P. vivax* resistance to chloroquine (erythrocytic forms) in Timor have been spread by a physician working for a private pharmaceutical company. Despite carefull examination of the duplicate slides, both in the Jakarta Malaria Reference Laboratory and in the Epsom WHO Malaria Reference Laboratory (England), no parasites could be found in the slides said to show resistant parasites.

In October 1973 a Government USA–NAMRU team[4] visited exactly the same area. The WHO sensitivity test was carried out. All *P. vivax* and *P. falciparum* cases responded satisfactorily to chloroquine (1500 mg base). In fact *P. vivax* parasites disappeared within 48 hours in the 15 cases investigated and even within 24 hours in 11 of them, after receiving only the first 10 mg/kg base chloroquine. *P. falciparum* asexual forms also disappeared within 72 hours in the 33 cases studied. The extended 28 days test was not carried out.

WHO sensitivity tests were also carried out in North Sumatra by another Government/ USA–NAMRU team. Results were similar with no evidence of resistance in *P. falciparum* or *P. vivax*.

The following case history is therefore the first documented report of 4-aminoquinolines resistance in a strain of *P. falciparum* from Indonesia.

THE CASE HISTORY

A patient with repeated P. falciparum recrudescences after radical treatment.

The patient Paryadi, a young adult male, age 20, weight 58 kg, was found positive *(P. falciparum)* on 17 May 1973 in Bantul Regency (Yogyakarta Province) shortly after returning from Kalimantan.

He was given a standard radical treatment of 1500 mg of amodiaquine base and 45 mg primaquine over a period of 3 days, from May 18 to May 20.

1. WHO Medical Officer, Indonesia.
2. Chief Malaria Control Programme, Indonesia.
3. Peters, W. (1970) Chemotherapy and Drug Resistance in Malaria, Academic Press.
4. Cyrus and Gundel finger, personal communication.

On June 18 he was found again positive and given a second standard radical treatment from June 23 to June 25.

On July 13 he was again found positive and given a third similar radical treatment but this time the amodiaquine was given and swallowed in the presence of the WHO malariologist. Duplicate slides were collected and the parasite count was carried out.

On August 7 he was again found positive and given a fourth radical treatment from August 10 to August 12.

On September 1st he was once more positive. This time 1500 mg chloroquine base were given and swallowed in the presence of the WHO malariologist. Duplicate slides were collected and the parasite count was carried out.

On September 27 he was once again found positive. Treatment was postponed to allow the isolation of the strain with the assistance of NAMRU.

A summary of the drugs given is shown in Table 1. Over a period of 5 months from May 17 to October 14 the patient has received a total of 12450 mg 4-aminoquinolines base (10350 mg amodiaquine and 2100 mg chloroquine), 350 mg pyrimethamine and 225 mg primaquine.

Table 1. Summary of treatments given to patient Paryadi

Date		Parasites	Drug doses (in mg base)				Remarks
			amodiaquine	pyrimethamine	primaquine	duration	
May	10	Negative	450	50	–	Single dose	Systematic
,,	17	F ++	450	50	–	Single dose	Symptomatic
,,	18-20	–	1500	–	45	3 days	
June	18	F +++Fg++	450	50	–	Single dose	Symptomatic
,,	23-25	–	1500	–	45	3 days	
July	2	Negative	450	50	–	Single dose	
,,	13	*	450	50	–	Single dose	Symptomatic
,,	19-24	*	1500	–	45	6 days	Amodiaquine given by WHO Malariologist
Aug.	1	*	–	50	–	Single dose	
,,	7	*	600	–	–	Single dose	Symptomatic
,,	10-15	*	1500	–	45	6 days	
Sept.	1	*	450	50	–	Single dose	Symptomatic
,,	3	*	600	–	–	Single dose	
,,	5-10	*	1500 (chloroquine)	–	45	6 days	Chloroquine given by WHO Malariologist
,,	29	*	450	–	–	Single dose	
Oct.	13	F++	600 (Chloroquine)	–	–	2 days	
,,	22	F+	–	50	–	Single dose	with 1000mg sulfadoxine

* : see details in following table

Particulars on drug tablets :

amodiaquine = Camoquin, Parke-Davis, 150 mg base
pyrimethamine = Daraprim, Burroughs-Wellcome, 25 mg
primaquine = Primaquine, Parke-Davis, 15 mg
chloroquine = Nivaquine, Specia, 100 mg base
sulfadoxine = Fansidar, Roche, 500 mg plus 25 mg pyrimethamine

The fact that the treatment (in addition to the doses given by the WHO malariologist) was given by a responsible supervisor living in the same Kampung, the rapid disappearance of the asexual forms after the schizontocidal treatment, the rapid disappearance of the gametocytes after the primaquine treatments, indicate that most, if not all, of the drugs were taken.

The infection was terminated by a single dose of the combination of 1.0 g of sulfadoxine and of 50 mg of pyrimethamine on 22 October.

Previously on 12 October blood samples were taken from the patient to be sent, through Taipei NAMRU–TAMU Research Units, to Bethesda US Naval Hospital for inoculation into volunteers. Unfortunately these samples were lost between Taipei and Washington.

The sensitivity tests.

1. Amodiaquine.

After having received on July 13 a presumptive treatment including 450 mg amodiaquine base and 50 mg pyrimethamine the patient, with an already low asexual parasitaemia, was given the standard amodiaquine dose by the WHO malariologist. The asexual forms rapidly disappeared but on day 19, the patient was found again with a high para-

Table 2. Results of test for P.falciparum strain sensitivity to a standard dose of amodiaquine in patient Paryadi.

Date		Day	Parasites: Trophozoites Count *	Trophozoites per mm^3	Gametocytes Count *	Gametocytes per mm^3	Drug dose (mg base)		Remarks
July	13	7	196	1372	0	0	amodiaquine pyrimethamine	450 & 50	Symptomatic
,,	19	0	15	105	1	7	amodiaquine	600	amodiaquine
,,	20	1	9	63	8	56	amodiaquine	600	given by WHO
,,	21	2	0	0	20	140	amodiaquine	300	malariologist
,,	22	3	0	0	30	210	primaquine	15	
,,	23	4	–	–	–	–	primaquine	15	
,,	24	5	0	0	20	140	primaquine	15	
,,	25	6	0	0	4	28			
,,	26	7	0	0	0	0			
,,	27	8	0	0	0	0			
,,	28	9	0	0	0	0			
,,	29	10	0	0	0	0			
,,	30	11	0	0	0	0			
,,	31	12	0	0	0	0			
Aug.	1	13	0	0	0	0	pyrimethamine	50	
,,	2	14	0	0	0	0			
,,	3	15	0	0	0	0			
,,	4	16	–	–	–	–			
,,	5	17	–	–	–	–			
,,	6	18	–	–	–	–			
,,	7	19	1440	10080	0	0	amodiaquine	600	Sick since 5 August.
,,	8	20	–	–	–	–			
,,	9	21	–	–	–	–			
,,	10	22	55	385	0	0	amodiaquine	600	
,,	11	23	0	0	2 only seen in thick film		amodiaquine	600	
,,	12	24	0	0	1 only seen in thick film		amodiaquine	300	

* : count per 1000 leucocytes

Conclusion : RI resistance, delayed recrudescence.

sitaemia (10.000 trophozoites per mm^3).

Details. including the action of the primaquine on the gametocytes, are given in Table 2 and are illustrated in Fig. I.

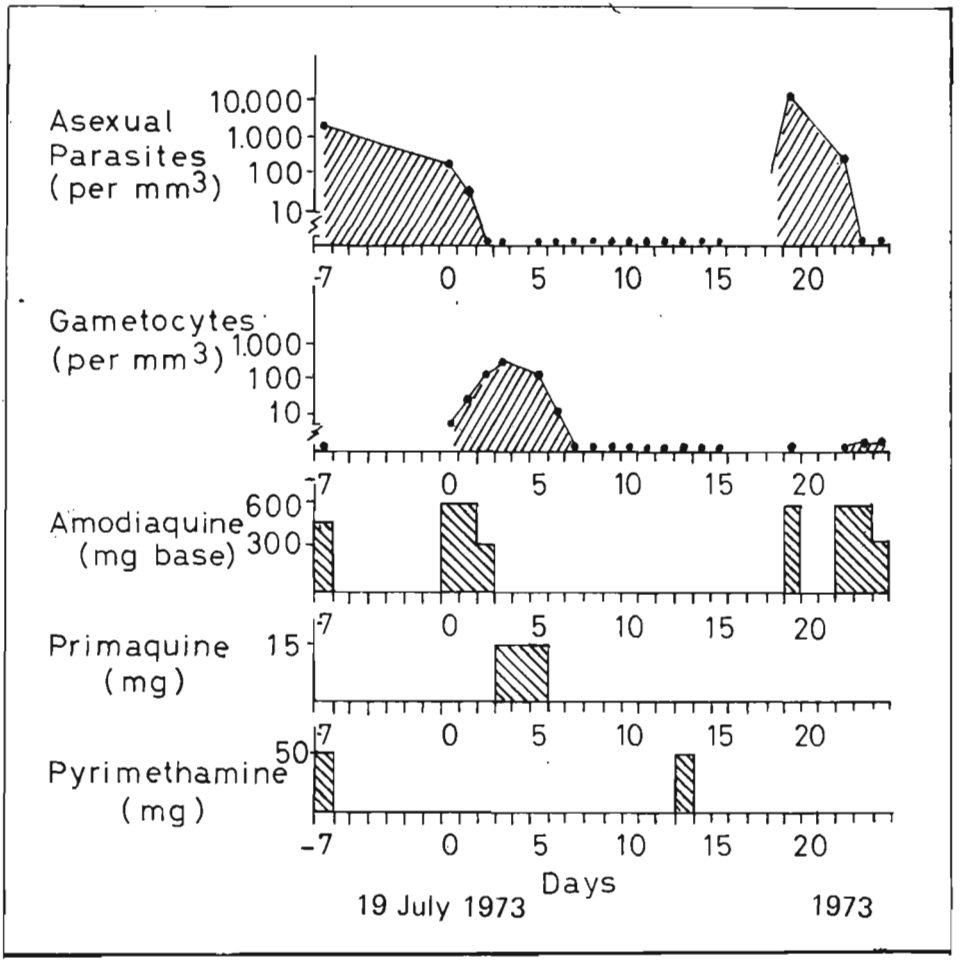


Fig.I. Effect of Amodiaquine, Primaquine & Pyremethamine on a P. falciparum from Samarinda (Kalimantan, (formerly Borneo).

2. Chloroquine.

After having received on September 1 and 3 respectively 450 mg amodiaquine base plus 50 mg pyrimethamine and 600 mg amodiaquine base, the patient, with an already low asexual parasitaemia, was given the standard chloroquine dose by the WHO malariologist. The remaining asexual forms disappeared very rapidly but on day 22 the patient was found again with a moderate parasitaemia (1000 trophozoites per mm3). Details are given in Table 3 and are illustrated in Fig II.

Table 3. Results of test for P. falciparum strain sensitivity to a standard dose of amodiaquine in patient Paryadi.

Date		Day	Parasites				Drug dose (mg base)		Remarks
			Trophozoites		Gametocytes				
			Count *	per mm^3	Count *	per mm^3			
Sept.	1	- 4	450	3150	0	0	amodiaquine pyrimethamine	450 50	Sick
„	2	- 3	–	–	–	–			
„	3	- 2	50	350	0	0	amodiaquine	600	
„	4	- 1	15	105	0	0			
„	5	0	3	21	1 only seen in thick film		chloroquine	600	chloroquine given by WHO malariologist
„	6	1	0	0	1 only seen in thick film		chloroquine	600	
„	7	2	0	0	2 only seen in thick film		chloroquine	300	
„	8	3	0	0	3	21	primaquine	15	
„	9	4	0	0	2	14	primaquine	15	
„	10	5	0	0	1 only seen in thick film		primaquine	15	
„	11	6	0	0	2 only seen in thick film				
„	12	7	0	0	1 only seen in thick film				
„	13	8	–	–	–	–			
„	14	9	–	–	–	–			
„	15	10	0	0	0	0			
„	16	11	–	–	–	–			
„	17	12	–	–	–	–			
„	18	13	0	0	0	0			
„	19	14	–	–	–	–			
„	20	15	–	–	–	–			
„	21	16	0	0	0	0			
„	22	17	–	–	–	–			
„	23	18	–	–	–	–			
„	24	19	0	0	0	0			
„	25	20	–	–	–	–			
„	26	21	–	–	–	–			
„	27	22	110	770	0	0			asymptomatic (except headache)
„	28	23	–	–	–	–			
„	29	24	45	315	0	0	amodiaquine	450	
„	30	25	15	105	0	0			
Oct.	1	26	5	35	0	0			
„	2	27	8	56	0	0			Treatment delayed for strain isolation
„	3	28	3	21	0	0			
„	4	29	4	28	0	0			
„	5	30	2	14	4	28			

* : count per 1000 leucocytes

Conclusion : RI resistance, delayed recrudescence.

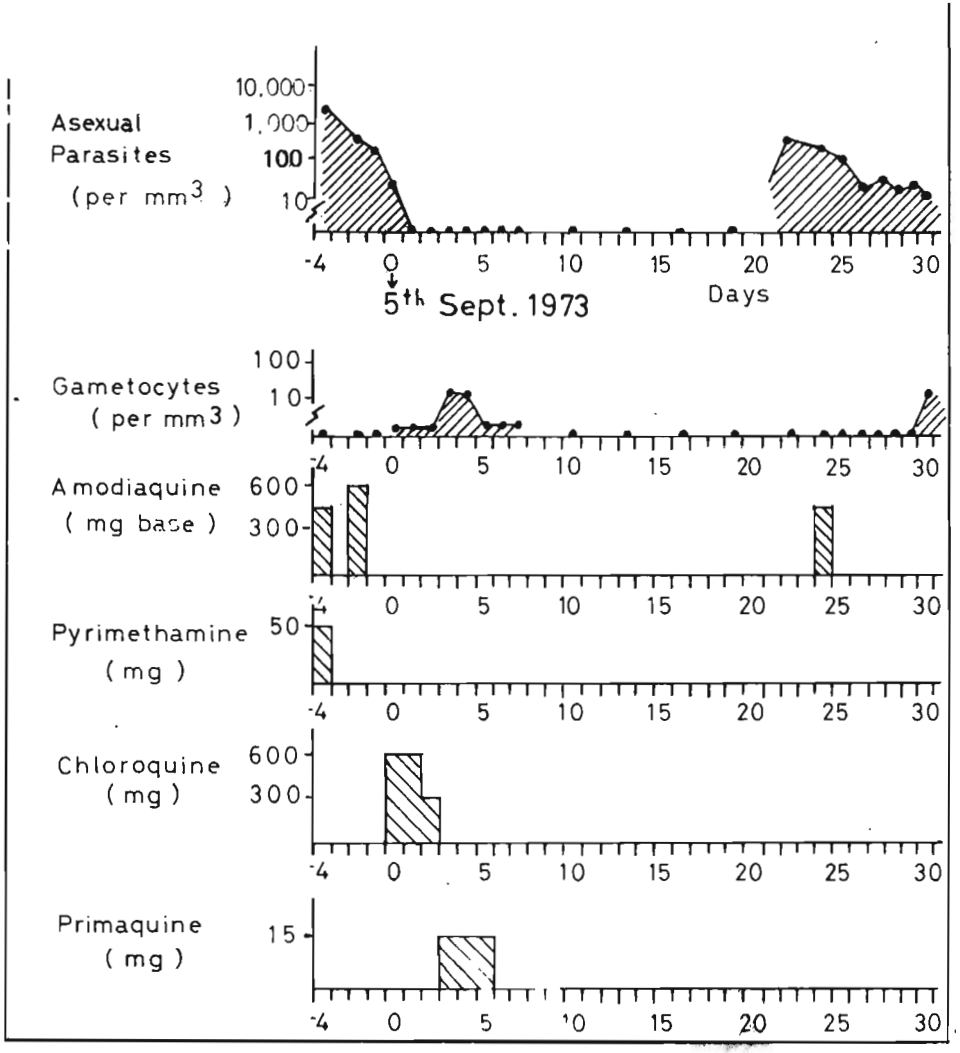


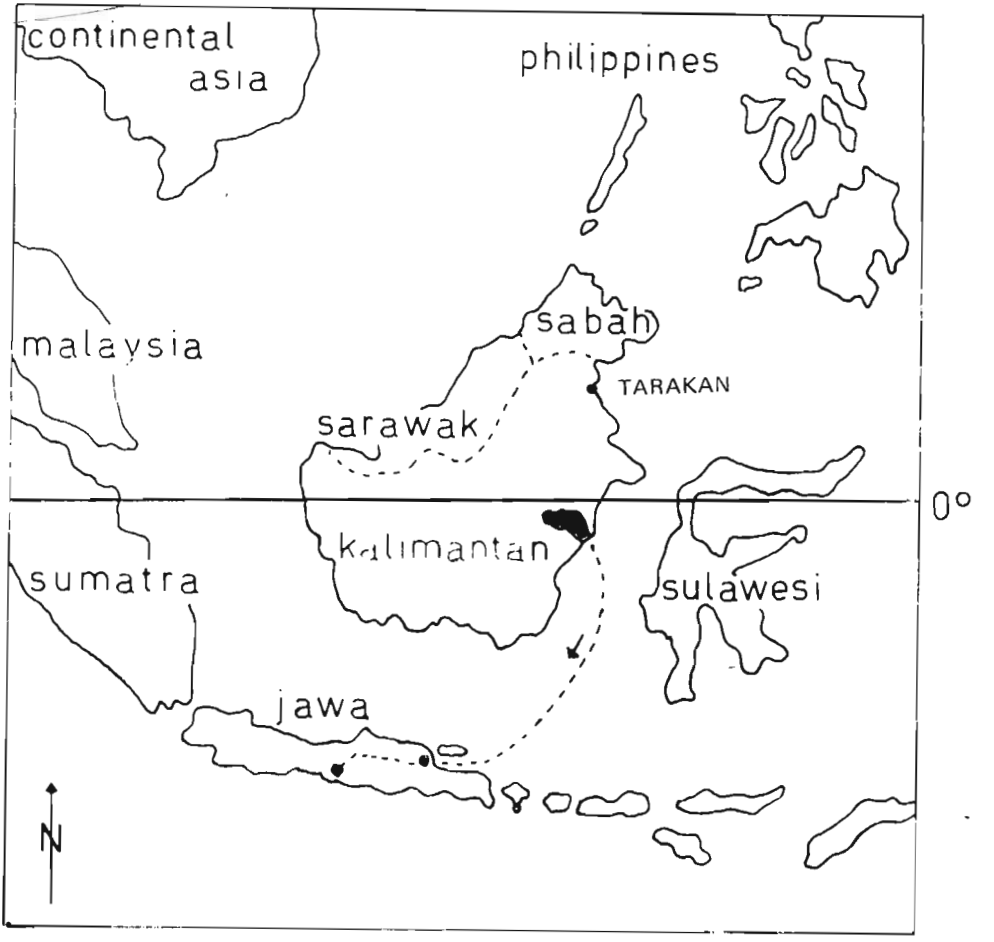
Fig. II. Effect of Amodiaquine, Pyrimethamine, Chloroquine & Primaquine on a P. falciparum Strain from Samarinda (Kalimantan, formerly Borneo).

No urine test was carried out as there was no Mayer-Tanret reagent available in the Province, but there was neither vomiting nor diarrhea.

The parasite counts were carried out by the WHO laboratory specialist, Mr. W. Rooney.

Origin of the case

The patient from Kampung Gedongan (Yogyakarta Province, Java), left his village for Kalimantan island in April 1972 and returned on 5 May 1973. The trip was made by bus to Surabaya, then by boat to Samarinda (Fig. III).



area in which infection occurred

itinerary followed by reported case from Samarinda to Yogyakarta via Surabaya.

Fig. III. Map of Indonesia

In Kalimantan the patient worked for 2 private Indonesian companies, Semogaraya and Batutipang Co., building bridges and schools. He stayed first on the outskirts of Samarinda then in Loa Janan and Segiri Kecamatan. In Loa Janan he worked in a forest area which can be reached by riverboat and foot in 2 hours from Samarinda and where he experienced at least 3 severe attacks of fever which were treated by injections and tablets. Other symptoms were headache, rigor, sweating but no vomiting.

There is no malaria control in this area control measures in Indonesia being mostly

limited to the islands of Java and Bali. On the other hand Kampung *Gedongan* in Yogyakarta Province, is located in a special study area which is sprayed twice a year with DDT and where an effective surveillance system is maintained, including active case detection, passive case detection and epidemiological investigations. This mechanism, which also includes the systematic examination of persons returning from other Provinces, revealed, in addition to one imported *P. vivax* case from Gunung Kidul in August, 2 other cases in 1973.
Two other cases found in the same Kampung.

The other two cases detected in Kampung Gedongan, Poniman and Amad Jumeri are 2 friends of the patient. They also went to Kalimantan and worked approximately in the same area but within a shorter period (five months).

Both were detected on 10 May, five days after their return from Kalimantan, and both were found positive for *P. vivax*. parasites.

The interesting fact is that both had recrudescences of *P. falciparum* after receiving radical treatment for *P. vivax*. Further recrudescences occurred after repeated radical treatments and the infections had to be terminated with the association sulfadoxine and pyrimethamine.

Both cases were obviously mixed infections with *P. vivax* predominating and resistant RI *P. falciparum* appearing only after the radical cure of *P. vivax*. In one (Achmad Jumeri) *P. falciparum* rings started to appear 2 days after the completion of the 14 days course of primaquine.

It is also significant to note that there has been no similar recrudescences detected amongst other imported or indigeneous cases followed up in the special study area of the Province of Yogyakarta. On the other hand *P. falciparum* resistant strains have already been confirmed in Sabah, located north of East Kalimantan (see map). One imported resistant case from Tarakan has also been mentioned by Van Dijk (personal communication).

Further studies will be carried out to delineate the infected area of Kalimantan, to identify the vector (which as in Sabah could be *A. b. balabacensis)* and to take remedial measures.

SUMMARY AND CONCLUSION

The first case of *P. falciparum* resistance to 4-aminoquinolines is reported from Indonesia.
After a normal initial response the asexual parasites were found to be resistant at the RI level to a standard regimen of 1500 mg amodiaquine base and to a standard regimen of 1500 mg chloroquine base.

The infection was contracted near Samarinda, east of Kalimantan (formely Borneo).

ACKNOWLEDGEMENTS

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